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(71) Applicant *(for all designated States except US)*: **NICOX S.A.** [FR/FR]; 2455, route des Dolines, Espace Gaia II - Bâtiment I, F-06906 Sophia Antipolis Cedex (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ONGINI, Ennio** [IT/IT]; Via Fratelli Cervi, Residenza Sorgente, I-20090 Segrate, Milano (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza, Milano (IT).

(74) Agents: **SAMA, Daniele** et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).

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(54) Title: NITRATE ESTER DERIVATIVES USEFUL FOR PREPARING DRUGS FOR EPILEPSY

(57) Abstract: Nitrooxyderivative compounds or salts thereof having the following general formula (I): $A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2$ (I) wherein: c0 is an integer and is 0 or 1, b0 is an integer and is 0 or 1, A = R-T_1-, wherein R is the radical of formula (II) as defined in the application; B is such that its precursor is selected from aminoacids, hydroxyacids, polyalcohols, compounds containing at least one acid acid function, C is a bivalent radical containing an aliphatic, heterocyclic or aromatic radical.

NITRATE ESTER DERIVATIVES USEFUL FOR PREPARING DRUGS FOR EPILEPSY

* * * * *

The present invention relates to drugs for the epilepsy treatment.

Epilepsy is defined as a group of cerebral disorders which appear with sudden and transitory episodes (fits or attacks) of abnormal phenomena having a motor origin (convulsions). The epileptic fits are characterized by patient consciousness loss and often accompanied by convulsions which in the most serious cases are extended to the musculature of the whole body.

Epilepsy has a high incidence in the population, only in the United States patients are 2.5 millions and every year about 100,000 new cases are diagnosed.

A classification of said disease based on clinical symptoms of the epileptic fits and on the state of the encephalographic trace is the following:

1) Partial fits (simple, complex or partially generalized) which appear with convulsions limited to only one limb or to a group of muscles; generally there is not consciousness loss even though in some cases (complex partial fits) episodes of confused behaviour appear.
2) Generalized fits which appear with consciousness loss episodes (epileptic absences) which can be accompanied by isolated clonic contractions (myoclonic fits), contractions of all the muscles, (clonic fits), generalized convulsions (tonic-clonic fits).

Epilepsy represents a serious social problem since this disease affects both the patient social relations and the working efficiency; in young people epilepsy influences not

only their insertion in the social organization but also the school efficiency.

Epilepsy is above all a serious sanitary problem: infact patients must take drugs for long periods (the therapy must be continued at least for two years after the fit disappearance). The drugs at present used, such for example phenobarbital, phenytoin, carbamazepine, in some patients are not able to control the convulsive activity and can interact with other drugs and, besides, cause side effects such as headache, nausea, vomit, sedation.

The need was felt to have available drugs for the epilepsy treatment effective in reducing the incidence and/or the seriousness of convulsive fits and having lower side effects.

It has now been surprisingly and unexpectedly found that said technical problem can be solved with the class of drugs which is described hereunder.

An object of the present invention are nitrooxyderivative compounds or salts thereof having the following general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

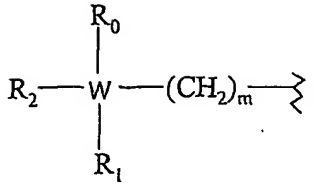
wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = R-T_1-, wherein

R is the radical of a precursor drug, having formula II:



(II)

wherein:

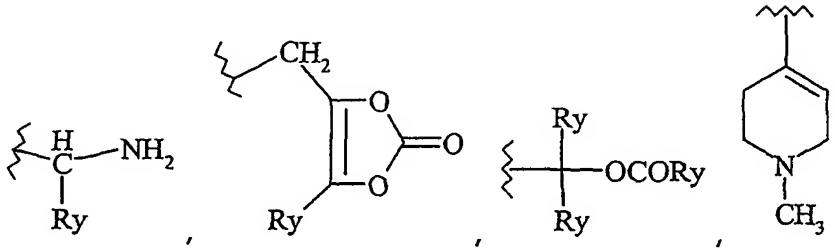
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

R_0 = H, $-(CH_2)_n-NHR_{1A}$, n being an integer from 0 to 2, wherein

R_{1A} = H, $-C(O)-R_{1H}$, $-C(O)O-R_{1H}$, wherein

R_{1H} is a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



(II-B) (II-C) (II-D) (II-E)

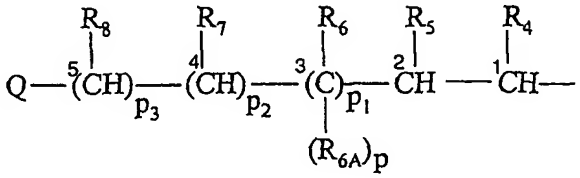
wherein Ry is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

R_1 = H, when W = N, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted;
- amidino group: $H_2N(C=NH)-$;

the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

wherein:

p, p_1, p_2 are integers, equal to or different from each other and ar 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1-C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1-C_6 alkyl,
- C_3-C_6 cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:
  - linear or branched C_1-C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
  - phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_{6A} = H, methyl;

R_6, R_{6A}, R_7, R_8, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type is present, between C_1 and C_2, R_4 and R_5 are free valences such as to form the double bond between C_1 and C_2; when the unsaturation is between C_3 and C_4, R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4; when the unsaturation is between C_4 and C_5, R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups:

$-OCH_3$, $-CF_3$, nitro; or Q can have one of the following meanings:

- C_3-C_6 cycloalkyl
- linear or branched C_1-C_6 alkyl
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) R_2 with R_1 and with W = C taken together form a C_4-C_{10}, preferably C_6 saturated or unsaturated, preferably saturated ring;

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = $-T_B-X_2-T_{B1}-$ wherein

T_B and T_{B1} are equal or different;

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B $-T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with

$-N(Z^I)(Z^{II})$, being:

- Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible,
- Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined is preferably selected in the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, slected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic alcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethyl alcohol, coniferyl alcohol, allopurinol;

- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein:

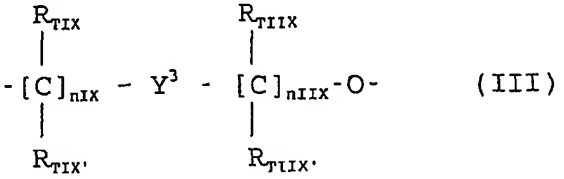
when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

when b0 = 0 : T_c = (CO) when t = 0, T_c = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, T_{BI} = X = —O—;

Y has one of the following meanings:

Y_p :



(III)

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from one to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected among nitrogen, oxygen, sulphur;

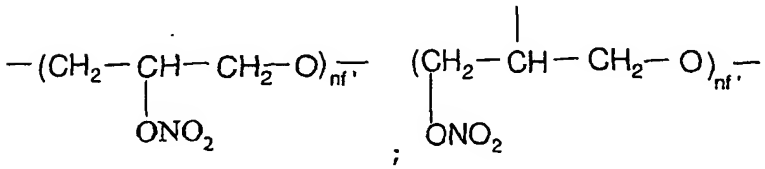
or Y can be:

Y_0, selected from the following:

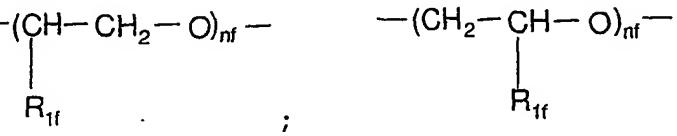
- an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from

5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

- 

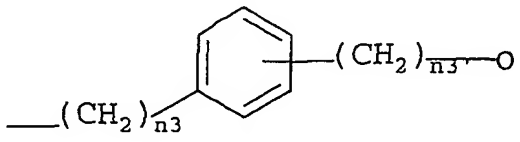
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 2 to 4;

- Y_{AR}, selected from:

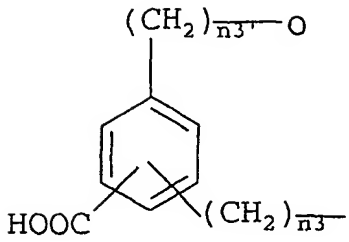
Y_{AR1}:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

- Y_{AR2}:



(VI)

wherein n3 and n3' have the above meaning.

When in formula (II) W = C, m = 1 and R_0 = $-(CH_2)_n-NH_2$ with n = 1, R_2 and R_1 with W as above form together the cyclohexane ring, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;

when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;

when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;

when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the thioguanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;

when in formula (II) W = C, m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

when in formula (II) W = C and has configuration (S), m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturatd with OH, the precursor drug of R is known as (S)3-isobutylGABA;

when in formula (II) W = C, m = 1 and R_0 = R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;

when in formula (II) W = C, m = 2 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrine;

when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical 3-4 di-hydroxy substituted benzyl, T_1 = CO and the free valence of A is saturated with OH, the percursor drug of R is known as 2-amino, (3,4-dihydroxyphenyl)propanoic acid (dopa).

Generally the precursor drugs of R are synthesized according to the methods reported in "The Merck Index, 12th Ed." (1996). When the precursor drugs of R comprise in the

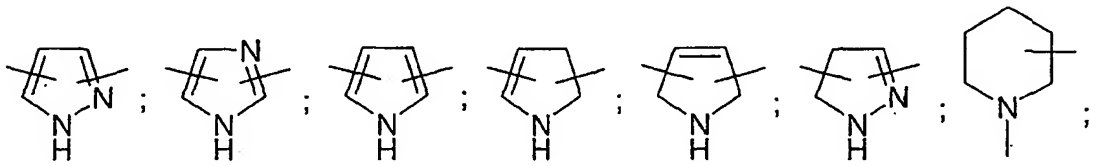
molecule the radical of formula (IIa), they can be synthesized as described in patent application WO 00/79658.

The precursor compounds of B of the above groups are prepared according to the methods known in the prior art and are described, for example, in "The Merck Index, 12th Ed." herein incorporated by reference.

Preferably when in formula (I) b0 = 0, Y in the bivalent linking group C is selected between Y_p and Y_{AR} as above.

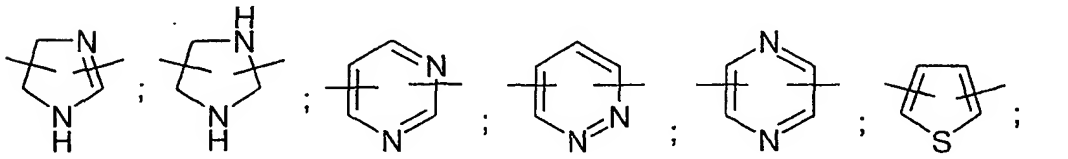
Preferably Y^3 is selected from the following bivalent radicals:

Preferably Y^3 is selected from the following bivalent radicals:

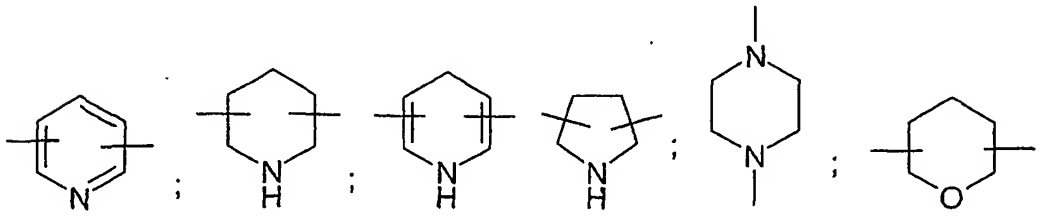


(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)

(Y19)



(Y7) (Y8) (Y9) (Y10) (Y11) (Y18)



(Y12) (Y13) (Y14) (Y15) (Y16) (Y17)

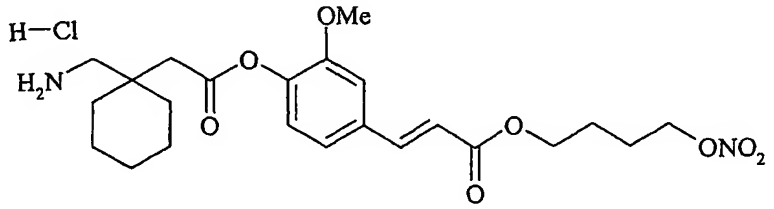
The preferred of Y^3 are the following: (Y12), having the two free valences in the ortho position with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted; (Y19), wherein the free valence on the ring is found in para position to the nitrogen atom.

The precursors of Y as defined in formula (III), wherein the free valence of the oxygen is saturated with H and the free valence of the end carbon is saturated either with a caraboxylic or a hydroxyl group, are products available on the market or can be obtained by methods known in the prior art.

In formula (I) the preferred precursors of B for the synthesis of the nitrooxyderivatives usable in the present invention are the following: ferulic acid, N-acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid; the preferred precursor drugs are the following: gabapentin, norvaline, arginine, pregabaline, (S)3-isobutylGABA, agmatine.

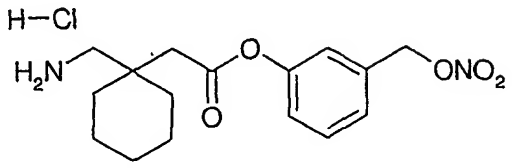
The preferred compounds of formula (I) according to the present invention are the following:

1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



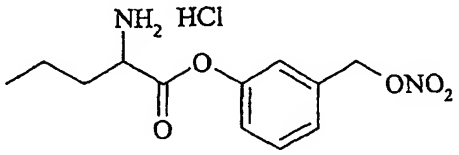
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



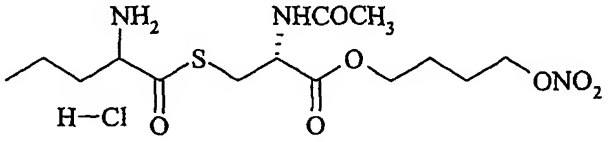
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



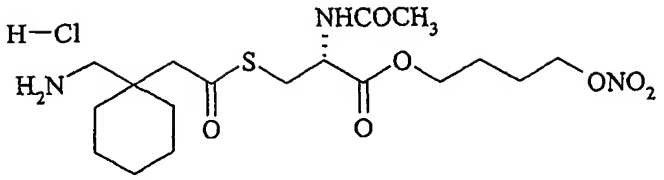
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino pentanoate hydrochloride (XVIII)



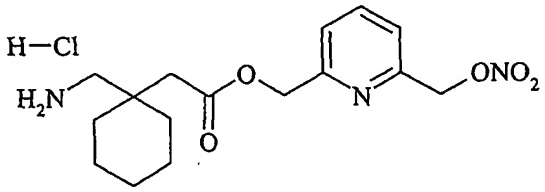
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl)cyclohexanacetate hydrochloride (XIX)



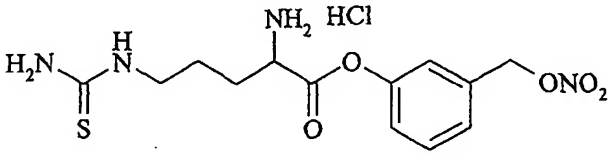
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



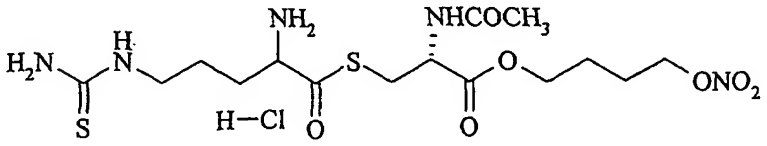
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



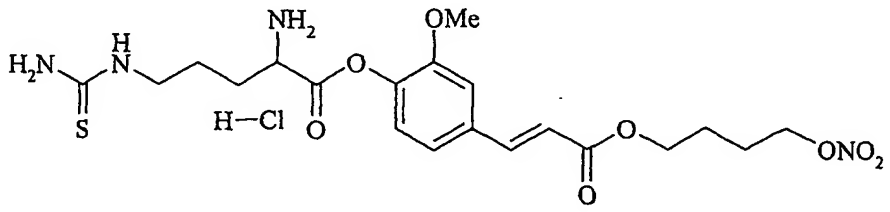
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



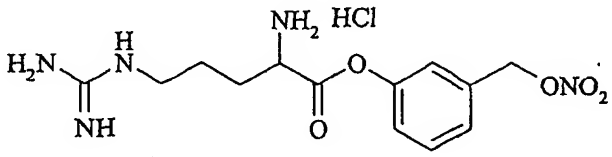
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



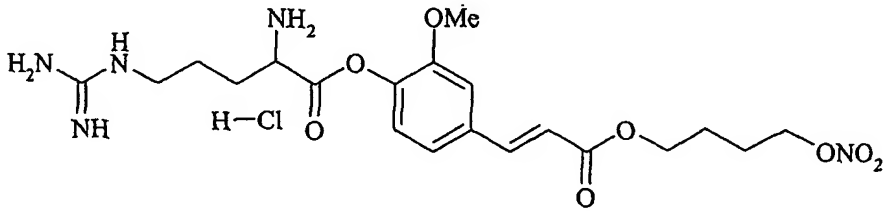
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



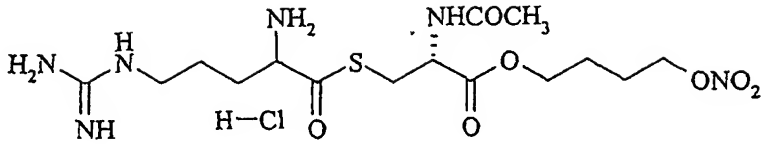
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E)- 3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



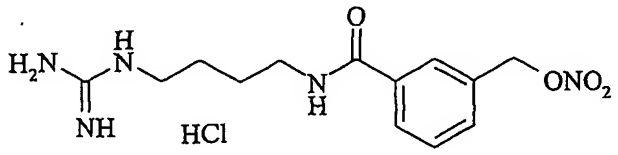
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



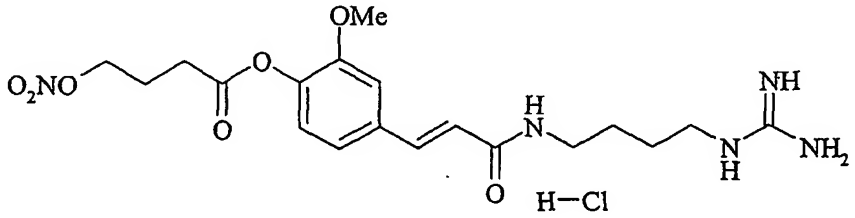
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



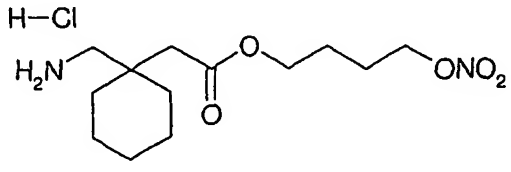
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)]phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy)butyl hydrochloride ester (XXIX)



(XXIX)

The preferred above mentioned compounds with the formulas (XV)- (XXIX) can be used as nitrate salts.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran with an equimolar amount of the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Salts with nitric acid are preferred.

The compounds of the invention have shown to have an improved activity with respect to the precursor drugs in the epilepsy treatment.

To evaluate the efficacy in the epilepsy treatment of the compounds of the present invention, one of the following pharmacological tests were used.

I) Limbic convulsions induced by pilocarpine (De Sarro G.B. et al. Eur. J. Pharmacol. 349: 179-185, De Sarro G.B., Brain Res. 591: 209-222, Turski W.A., Behav. Brain Res., 9: 315-336).

Male Sprague-Dawley rats weighing 280-350 g were used; they were subcutaneously injected with 1 mg/Kg of scopolamine. 15 minutes later, to the groups of animals the tested nitrooxyderivatives and the corresponding precursor drugs, dissolved in sterile saline solution were respectively administered by intraperitoneal injection. After one hour from the scopolamine injection, pilocarpine hydrochloride,

dissolved in saline solution, was administered by intraperitoneal injection at the doses of 200 or 350 mg/kg.

At the end of the treatments the animals were placed in circular Plexiglass cages (40 cm diameter.) For a time of 180 minutes after the administration of pilocarpine hydrochloride, the onset time and the intensity of the convulsions were checked.

The response of each animal was rated on the basis of a score assigned according to the scheme:

0 no reaction
1 perioral movements and scratching
2 tremors and relaxation of the hind paws
3 head movements and/or animal walking backwards
4 animal rising on the hind paws and tremors of the fore paws
5 falls
6 diffused tremors in the whole body
7 tonic clonic convulsions.

Method by analysis of the electroencephalographic tracing.

In this experiment were used mice belonging to a lethargic mice stock (Lh/Lh) which, when aged of about 15 days develop an ataxic behaviour (Hosford DA Adv Neurol. 1999; 79: 239-252).

The animals, between 11 and 17 weeks old, were anaesthetized with ketamine (7.5 mg/g, i.p.) and medetomidine (0.1 mg/100 g, i.p.). In the frontal cortex and in the parietal cortex (0.8 mm under the dura mater) of each animal two microelectrodes connected to an apparatus for recording the electroencephalographic trace and to a cannula for administering the compounds were inserted.

Once a week, counted by the insertion of the electrodes, an electroencephalographic trace of 2 hours was recorded.

After 15 minutes from the registration of the basic tracing, to the groups of mice solutions of the compounds, the corresponding precursor drugs in sodic phosphate buffer (67 mM) and the carrier were respectively administered by intracerebral infusion (2.5 µl/min for a total volume of 10 µl).

After the pharmacological treatment the electroencephalographic tracing was recorded for 3 hours and the animals were kept under observation for checking behaviour changes.

Absences were quantified on the basis of the duration of the spike discharges on the electroencephalogram as described by Hosford DA et al. Science, 1992 Jul 17; 257(5068): 398-401 (variations of the electroencephalographic trace of amplitudes not lower than 60 µV and of frequencies in the range 5-6 Hz were recorded, attacks must last not less than 0.6 sec).

The electroencephalographic tracing were recorded by amplification of 200-300 µV/cm and with a paper speed of 3 mm/sec.

In order to test the pharmacological effect of the compounds, each electroencephalographic tracing of 3 hours was divided into sections of 30 minutes and for each section the total duration of the spike and wave discharges was calculated; it was then normalized dividing this value by the corresponding value obtained after the administration of the vehicle.

II) Evaluation of anticonvulsant activity in DBA/2 mice after auditory stimulation

Groups of DBA/2 mice (weight 6 to 12 g, 22-26 days old) were treated with testing compounds. All compounds were given intraperitoneally (i.p.) dissolved in sterile saline solution 60 min prior of exposing mice to auditory stimulation. For each dose of compounds studied against audiogenic seizure 10 mice were used.

Each mouse was placed under a hemispheric perspex dome (diameter 58 cm) and left for 1 min in order to allow habituation and assessment of locomotor activity. Auditory stimulation (12-16 kHz, 109 dB) was applied for 1 min or until tonic extension occurred. Seizure response was assessed according to De Sarro GB et al. Neuropharmacology, 23(5):525-30, 1984) using the following scale: 0 = no response, 1 = wild running, 2 = clonus, 3 = tonus, 4 = respiratory arrest. The maximum response was recorded for each animal. Rectal temperature was recorded immediately prior to auditory testing using an Elektrolaboratoriet thermometer type T.E.3. Behavioural changes were monitored during period between drug administration and auditory testing.

III) Evaluation of anticonvulsant activity by convulsant agent pentylenetetrazole

Groups of ICR CD1 mice (weight 16 to 24 g, 42 to 48 days old) were treated with testing compounds to evaluate the pharmacological effects on subconvulsant (40 mg/kg) or convulsant (CD_{97} 85 mg/kg) dose of pentylenetetrazole was used. All compounds were administered intraperitoneally (i.p.), as above indicated, 60 min before a subcutaneous (s.c.) injection

of pentylenetetrazole (0.1 ml/10 g of body weight). All ICR CD1 mice were observed for 60 min. Animals were scored as seizure positive if they exhibited continuous limb clonus lasting 3 s or of longer duration. For each dose of compounds studied against pentylenetetrazole seizure 10 mice were used.

The compounds of the invention can also be used in combination with NO-donor compounds of the prior art.

The NO donor compounds which can be used in combination with the invention compounds must comply with the test in vitro defined hereinafter.

The test relates to the generation of nitric oxide from the NO donors, for example nitroglycerin, niocorandil, nitroprussiate, etc., in the presence of endothelial cells (method a) or platelets (method b).

a) Endothelial cells

Cells of the human umbilical vein, cultured on plates, having a 10^3 density cells/well were incubated for 5 minutes with scalar concentrations of NO donor (1-100 µg/ml). The incubation medium (physiologic solution, for example Tyrode) was then analyzed to determine the capability to generate NO of the compound under test, by means of:

1) nitric oxide detection by chemiluminescence;
2) cGMP determination (cyclic GMP n° 2715 of the above mentioned Merck).

For the analysis by chemiluminescence, an amount equal to 100 µl was injected in the reaction chamber of a chemiluminescence analyzer containing glacial acetic acid and potassium iodide. The nitrites/nitrates present in the medium, under these conditions, are converted into NO

which is then detected after reaction with ozone, which produces light. In the equipments measuring the chemiluminescence, the produced luminescence is directly proportional to the generated NO levels and can be measured by a suitable photomultiplying unit of a chemiluminescence analyzer. The photomultiplier converts the incident light into electric voltage, which is quantitatively recorded. On the basis of a calibration curve, prepared with scalar nitrite concentrations, it can be quantitatively determined the generated NO concentration. For example, from the incubation of 100 µM of nicorandil, an amount equal to about 10 µM of NO was generated.

For cGMP determination, an aliquot of the incubation medium (equal to 100 µl) was centrifuged at 1,000 revolutions for 20 seconds. The surnatant was removed and the sediment treated with iced phosphate buffer (pH 7.4). The produced cGMP levels were tested by specific immunoenzymatic reactants. From said experiments it resulted that, under these experimental conditions, the incubation with one of the various tested NO donors caused a significant increase of cGMP with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 µM of sodium nitroprussiate, an increase of about 20 times the value obtained with the incubation of the carrier alone, without NO donor was recorded.

b) Platelets

Washed human platelets, prepared substantially in the same way as described by Radomski et al, (Br. J.

Pharmacol. 92, 639-1987), were used. Aliquots of 0.4 ml were incubated for 5 minutes with NO-donor scalar concentrations (1-100 µg/ml). The incubation medium (for ex. Tyrode) was then analyzed to determine the capability of the tested compound to generate NO, by the determination of nitric oxide by chemiluminescence and the determination of cGMP, as described in the previous paragraph for the same analyses carried out on the endothelial cells. For the determination by chemiluminescence, also in this case, on the basis of a calibration curve prepared with scalar concentrations of nitrite, it was possible to quantitatively determine the produced NO amount. For example, after incubation of 100 µM of nicorandil, an amount equal to 35 µM of NO was generated.

For cGMP determination, it resulted that also under these experimental conditions the incubation with one of the tested NO donors gave a significant increase of cGMP with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 µM of sodium nitroprussiate, an increase of about 30 times the value obtaind with the incubation of the only carrier without NO donor took place.

The preferred NO-donor compounds are those which in the molecule contain radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen and are described in patent applications WO 95/20641, WO 97/16405, WO 95/09831, WO 01/12584.

The compounds of the present invention can be synthesized as follows.

Generally when in the drug molecule more reactive groups such as for example COOH and/or HX are present, they must be protected before the reaction according to the methods known in the prior art; for examaple as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The acylhalides are prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

1) When in formula (I) b0 = 0 and the free valence of the radical R of the drug is saturated with a carboxylic group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

1.A) The drug of formula RCOOH is treated with an agent activating the carboxyl group selected from N,N'carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide (DCC) in solvent such as for example DMF, THF, chloroform, etc., at a temperature in the range from -5°C to 50°C and reacted in situ with a compound HO-Y-Hal, wherein Y and Hal are as above defined.

$$RCOOH \xrightarrow{DCC,\ HO\text{-}Y\text{-}Hal} R\text{-}CO\text{-}O\text{-}Y\text{-}Hal \qquad (1C)$$

1.B) Alternatively, the drug acylhalide is reacted with a compound $HO\text{-}Y\text{-}R_{8A}$, wherein Y is as above, R_{8A} is OH or halogen in the presence of a base, in an organic solvent inert under the reaction conditions according to the scheme below reported:

$$RCOHal + HO\text{-}Y\text{-}R_{8A} \dashrightarrow R\text{-}COO\text{-}Y\text{-}R_{8A} \quad (1D)$$

1.C) When the compounds obtained in the above reactions have formula R-COO-Y-Hal the corresponding nitrooxyderivatives are obtained by reacting the compound R-CO-O-Y-Hal with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran according to the scheme:

$$R\text{-}COO\text{-}Y\text{-}Hal + AgNO_3 \dashrightarrow R\text{-}COO\text{-}Y\text{-}ONO_2$$

1.D) When the compounds obtained in the above reactions have formula R-COO-Y-OH the hydroxyl group is subjected to halogenation, for example with PBr_3, PCl_5, $SOCl_2$, PPh_3 + I_2, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

2) When in formula (I) b0 = 0, and the reactive function of the drug is the group NH_2, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

2.a) By reaction of the drug $R\text{-}NH_2$ with an acyl halide of formula Hal-Y-COHal, wherein Y and Hal are as above, according to the scheme:

$$R\text{-}NH_2 + Hal\text{-}Y\text{-}COHal \dashrightarrow R\text{-}NHCO\text{-}Y\text{-}Hal \quad (2A)$$

2.b) By reaction of the drug $R\text{-}NH_2$ with an acyl halide of formula OH-Y-COHal, wherein Y and Hal are as above, according to the scheme:

$$R\text{-}NH_2 + Hal\text{-}Y\text{-}COCl \dashrightarrow R\text{-}NHCO\text{-}Y\text{-}OH \quad (2B)$$

2.c) When the compounds obtained in the above reactions have formula R-NHCO-Y-Hal or R-NHCO-Y-OH the corresponding nitrooxyderivatives are obtained as above described in 1.C and 1.D respectively.

3. When in formula (I) b0 = c0 = 1, and the free valence of the radical R of the drug is saturated with a carboxylic

group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

3.a) Alternatively the acyl halide of the drug and the compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, are reacted according to the methods known in the prior art, to give the compound $R-CO-X-X_2-COOH$ which is transformed into the corresponding sodic salt and reacted with a compound of formula $Hal-Y-R_8$ wherein Hal and Y are as above and R_8 is Cl, Br, Iodine, OH:

$$R-COHal + HX-X_2-COOH \dashrightarrow R-CO-X-X_2-COOH \quad (3.A)$$

$$R-CO-X-X_2-COONa + Hal-Y-R_{8A} \dashrightarrow R-CO-X-X_2-CO-Y-R_{8A} \quad (3.A')$$

When R_{8A} = OH the compound of formula (3.A') is subjected to halogenation as above described in 1.D, when R_{8A} = Hal the compound of formula (3.A') is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

3.b) When Y_T is a C_4 linear alkylene, the precursor of B of formula $HO-X_2-COOH$ is reacted with triphenylphosphine in the presence of a halogenating agent such as CBr_4 or N-bromosucciniimide in tetrahydrofuran to give the compound of formula $HO-X_2-COO(CH_2)_4Br$ which is reacted with the molecule of the drug RCOOH as described in 1.A and 1.C.

4) When in formula (I) p = 1 b0 = c0 = 1, and the reactive function of the drug is the group NH_2, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

4.a) Reaction of the drug $R-NH_2$ with an acyl halide of formula $HX-X_2-COHal$, wherein X and X_2 are as above, according to the methods known in the prior art, to give the compound $R-NH-CO-X_2-XH$ which is reacted with a compound of formula $R_{8A}-Y-COHal$ wherein R_{8A} and Y are as above.

$R-NH_2 + HX-X_2-COCl \dashrightarrow R-NH-CO-X_2-XH$ (4.A)

$R-NH-CO-X_2-XH + R_{8A}-YCO-Hal \dashrightarrow R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4A')

4.b) Alternatively, the drug $R-NH_2$ is reacted with a compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, in the presence of dicyclohexylcarbodiimide as described in 1.A, to give the compound $R-NH-CO-X_2-XH$, which is reacted with a compound of formula $R_{8A}-Y-COCl$ wherein R_{8A} and Y are as above defined, to give the following compound: $R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4.B)

When R_{8A} = OH the compound of formula (4.B) or of formula (4a') is subjected to halogenation as above described in 1.D; when R_{8A} = Hal the compound of formula (4.B) is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

When the compounds in the present invention have one or more chiral centres, they can be in racemic form or as mixtures of diastereoisomers, enantiomers, as single enantiomers or single diastereoisomers; when the compound shows a geometric asymmetry the compounds in the cis or trans form can be used.

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral use, etc., according to the tchniques well known in the field, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15th Ed."

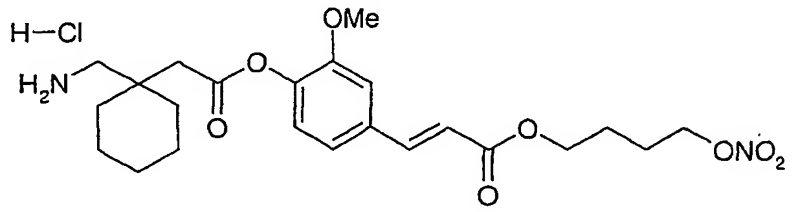
The amount on a molar basis of the active principle in said formulations is equal to or lower than the maximum posology indicated for the precursor drugs. Also higher doses can be used, considering their very good tolerability.

The administrable daily doses are those of the precursor drugs, or even lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following Examples illustrate the invention without limiting the scope thereof.

EXAMPLE 1

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl] phenyl hydrochloride ester (XV)



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid

To a solution of 1-(aminomethyl)cyclohexanacetic acid (10 g, 58.4 mmoles) in a mixture of dioxane (100 ml) and water (150 ml), triethylamine (16.27 ml, 116.8 mmoles) and di-tert-butyldicarbonate (15.3 g, 70 mmoles) are added. The reaction mixture is left at room temperature, under stirring for 4 hours. After having cooled the solution to 0°C it is brought to pH 2 with HCl 5%. The precipitate is filtered and dried under vacuum. 15 g of the expected compound are obtained as a white solid having m.p. = 125°-127°C.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmoles) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47

mmoles) and triphenylphosphine (31.34 g, 119.47 mmoles) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The residual crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Syntheis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-*propenyl*]*phenol*

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenol (8 g, 24.3 mmoles) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmoles) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

D) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 1-(N-tert-butoxycarbonyl aminomethyl) cyclohexan acetic acid (2.5 g, 9.2 mmoles) in chloroform (200 ml) and N,N-dimethylformamide (3 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl] phenol (3.15 g, 10.1 mmoles), dicyclohexylcarbodiimide (5.7 g, 27.6 mmoles) and N,N-dimethylaminopyridine (33 mg, 0.27 mmoles) are added.

The reaction mixture is left at room temperature, under stirring for 3 hours, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate

and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 5 g of the expected compound are obtained as an oil.

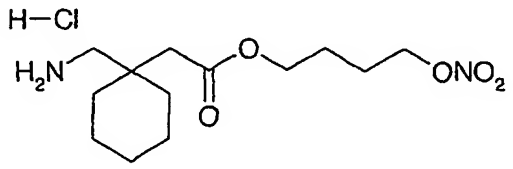
E) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl] phenyl hydrochloride ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl ester (5 g, 8.8 mmoles) in ethyl acetate (100 ml), a solution of HCl 1N in ethyl acetate (50 ml) is added. The reaction mixture is left overnight at room temperature, then concentrated under vacuum to a volume of 40 ml. The obtained residue is treated with ethyl ether. The precipitate is filtered and dried under vacuum. 1.8 g of the expected compound are obtained as a white solid having m.p. = 103°-105°C.

^{1}H-NMR ($CDCl_3$) ppm: 8.43 (2H, m); 7.55 (1H, d); 7.10 (3H, m); 6.34 (1H, d); 4.51 (2H, t), 4.26 (2H, t); 3.89 (3H, s); 3.12 (2H, s); 2.81 (2H, s); 1.82 (4H, m); 1.54 (10H, m).

EXAMPLE 2

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 4-(bromo)butyl ester

To a solution of 1-(N-tert-butoxycarbonyl aminomethyl)cyclohexan acetic acid (1 g, 3.6 mmoles) in N,N-dimethyl formamide (50 ml) cooled at 0°C, sodium ethylate (246 mg, 3.6 mmoles) is added.

The reaction mixture is left at 0°C under stirring for 30 minutes, and then 1,4-dibromobutane (1.28 ml, 10.8 mmoles) is added. The solution is left under stirring at room temperature overnight, then diluted with ethyl ether and washed with water. The organic phase dried with sodium sulphate is evaporated under vacuum. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.7 g of the expected compound are obtained as an oil.

B) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 4-(nitrooxy)butyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 4-(bromo)butyl ester (1 g, 2.5 mmoles) in acetonitrile (200 ml) silver nitrate (1.3 g, 7.5 mmoles) is added. The reaction mixture is heated at 80°C for 6 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.8 g of the expected compound are obtained as an oil.

C) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester

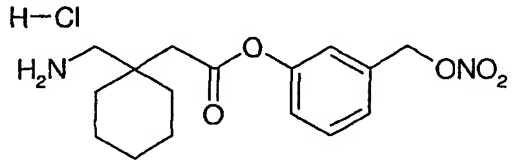
To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 4-(nitrooxy)butyl ester (0.8 g, 2.06

mmoles) in ethyl acetate (5 ml) a solution of HCl 1N in ethyl acetate (20 ml) is added. The reaction mixture is left for 3 hours at room temperature then it is treated with n-hexane. The precipitate is filtered and dried under vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 80.3°-81.3°C.

^{1}H-NMR (DMSO) ppm: 8.23 (2H, s); 4.58 (2H, t), 4.09 (2H, t); 2.92 (2H, s); 2.56 (2H, s); 1.74 (4H, m); 1.44 (10H, m).

EXAMPLE 3

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVI)



A) Synthesis of 3-(bromomethyl)phenol

To a solution of 3-hydroxybenzyl alcohol (4 g, 32.2 mmoles) in methylene chloride (250 ml), cooled at 0°C, tetrabromomethane (12.82 g, 38.6 mmoles) and triphenylphosphine (12.67 g, 48.3 mmoles) are added. The mixture is kept under stirring at 0° for 10 minutes, then evaporated at reduced pressure. The crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 3.5 g of the expected product are obtained.

B) Synthesis of the 1-(N-tert-butoxycarbonylamino-methyl)cyclohexan acetic acid 3-(bromomethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid (2.6 g, 9.7 mmoles) in chloroform (200 ml) and N,N-dimethylformamide (2 ml), 4-(bromomethyl)phenol (2g, 10.7 mmoles), dicyclohexylcarbodiimide (4 g, 19.7

mmoles) and N,N-dimethylaminopyridine (24 mg, 0.20 mmoles) are added. The reaction mixture is left at room temperature for 4 hours under stirring, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 1.4 g of the compound are obtained as an oil.

C) Synthesis of the 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(bromomethyl) phenyl ester (1.4 g, 3.18 mmoles) in acetonitrile (300 ml) silver nitrate (1 g, 6.36 mmoles) is added. The reaction mixture is heated at 50°C for 4 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.75 g of the expected compound are obtained as an oil.

D) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester

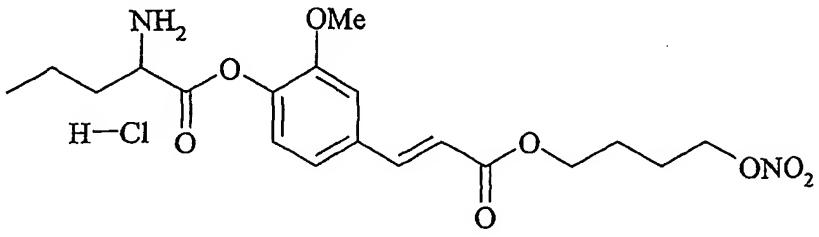
To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester (0.75 g, 1.8 mmoles) in ethyl acetate (5 ml), a solution of HCl 1N in ethyl acetate (18 ml) is added. The reaction mixture is left for 15 minutes at room temperature, then it is treated with n-hexane. The precipitate is filtered and dried under

vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 106°-108°C.

^{1}H-NMR (DMSO) ppm: 8.16 (3H, m); 7.52 (1H, t); 7.44 (1H,d); 7.34 (1H, s), 7.28 (1H, d); 5.65 (2H, s), 3.03 (2H, m); 2.86 (2H, s); 1.55 (10H, m).

EXAMPLE 4

Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylamino) pentanoic acid.

To a solution of 2-aminopentanoic acid (4 g, 34.14 mmoles) in dioxane (40ml) and water (75ml), triethylamine (9.5 ml, 68.29 mmoles) and di-tert-butyldicarbonate (8.94 g, 49.97 mmoles) are added. The reaction mixture is left at room temperature, under stirring for 17 hours. Afte having cooled the solution at 0°C it is brought to pH = 2 with HCl at 5%. One extracts with ethyl acetate, the joined organic phases are washed with water and dried with sodium sulphate.

The solvent is evaporated at reduced pressure to give the compound as an yellow oil which is used without further purification.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmoles) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47 mmoles) and triphenylphosphine (31.34 g, 119.47 mmoles) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The obtained crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Synthesis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenolo (8 g, 24.3 mmoles) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmoles) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

C) Synthesis of the 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid (0.5 g, 2.3 mmoles) in chloroform (12 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol (0.86 g, 2.76 mmoles), dicyclohexylcarbodiimide (0.52 g, 2.53 mmoles) and N,N-dimethylaminopyridine (0.03 g, 0.23 mmoles) are added. The reaction mixture is left at room

temperature for 1 hour under stirring, filtered and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 0.5 g of the expected compound are obtained as an oil. Yield 43%.

D) Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester (0.28 g, 0.548 mmoles) in ethyl acetate (7 ml), a solution of HCl in ethyl acetate (6.8 N, 0.700 ml) is added. The reaction mixture is left 3 hours at room temperature. The precipitate is filtered and dried under vacuum. 0.1 g of the expected compound are obtained as a white solid.

^{1}H-NMR (DMSO) ppm: 8.75 (3H, m); 7.62 (1H, d); 7.58 (1H, s); 7.3 (1H, d); 7.2 (1H, d); 6.72 (1H, d); 4.57 (2H, t), 4.26 (1H, t); 4.18 (2H, t); 3.82 (3H, s); 1.95 (2H, m); 1.75 (4H, m); 1.45 (2H, m) 0.98 (3H, m).

CLAIMS

1. Nitrooxyderivative compounds or salts thereof having the general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

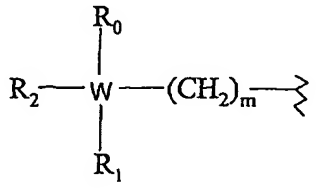
wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = $R\text{-}T_1$-, wherein

R is the radical of a precursor drug of formula II:



(II)

wherein:

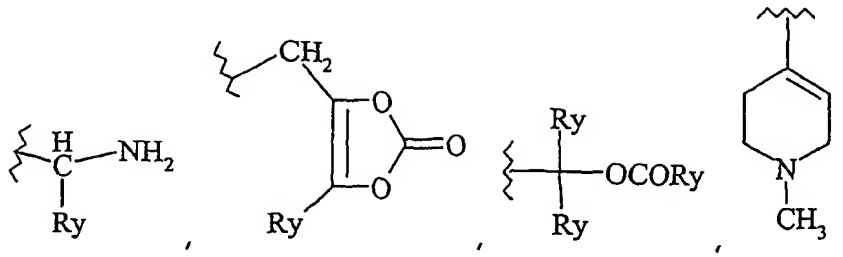
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

R_0 = H, $-(CH_2)_n\text{-}NHR_{1A}$, n being an integer from 0 to 2, wherein

R_{1A} = H, $-C(O)\text{-}R_{1H}$, $-C(O)O\text{-}R_{1H}$, wherein

R_{1H} is a linear or branched $C_1\text{-}C_{10}$ alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



(II-B) (II-C) (II-D) (II-E)

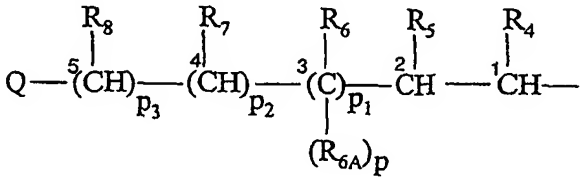
wherein Ry is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

R_1 = H, when W = N, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted;
- amidino group: $H_2N(C=NH)-$;

the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

wherein:

p, p_1, p_2 are integers, equal to or different from each other and are 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1-C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1-C_6 alkyl,
- C_3-C_6 cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:
  - linear or branched C_1-C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
  - phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_6, R_{6A}, R_7, R_8, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type is present, between C_1 and C_2, R_4 and R_5 are free valences such as to form the double bond between C_1 and C_2; when the unsaturation is between C_3 and C_4, R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4; when the unsaturation is between C_4 and C_5, R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups:

$-OCH_3$, $-CF_3$, nitro; or Q can have one of the following meanings:

- C_3-C_6 cycloalkyl;
- linear or branched C_1-C_6 alkyl;
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) R_2 with R_1 and with W = C taken together form a C_4-C_{10}, preferably C_6, saturated or unsaturated, preferably saturated ring;

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = $-T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI}= $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B $-T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with $-N(Z^I)(Z^{II})$, being:

Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible,

Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined is selected from the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetyl-penicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic polyalcohols, selectd from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl alcohol, allopurinol;
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein

when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

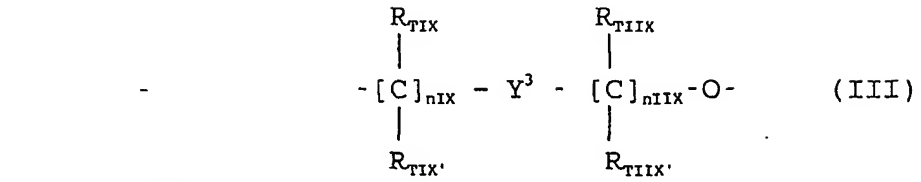
when b0 = 0 : T_c = (CO) when t = 0, T_c = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, T_{BI} = X = –O–;

T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above;

Y has one of the following meanings:

Y_p :



(III)

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

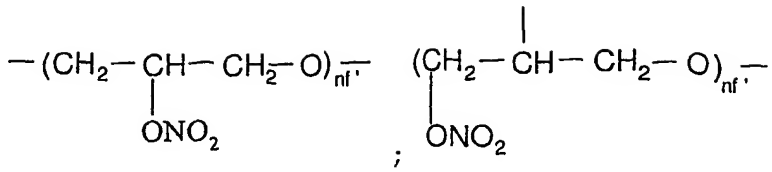
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from 1 to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

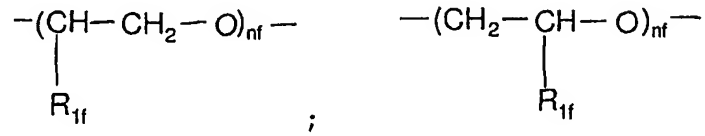
Y_0, selected from the following:

an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

- 

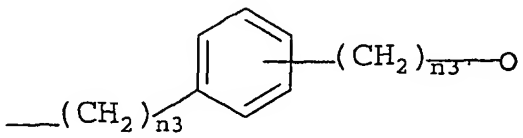
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 2 to 4;

Y_{AR}, selected from:

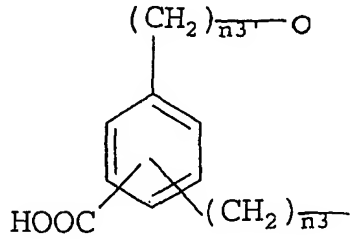
Y_{AR1}:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

Y_{AR2}:



(VI)

wherein n3 and n3' have the above mentioned meaning.

2. Compounds according to claim 1, wherein:

- when in formula (II) W = C, m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_2 and R_1 with W as above form together the cyclohexane ring, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;
- when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;
- when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;
- when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the thioguanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;
- when in formula (II) W = C, m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the

free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

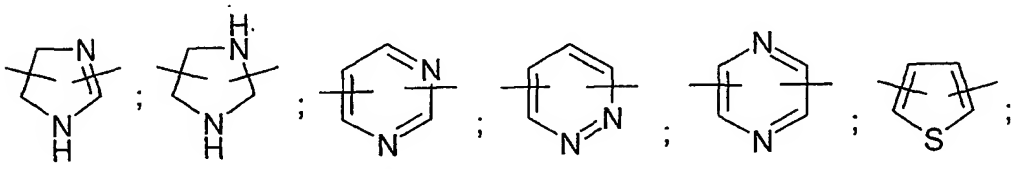
- when in formula (II) W = C and it has configuration (S), m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as (S)3-isobutylGABA;
- when in formula (II) W = C, m = 1 and R_0 = R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;
- when in formula (II) W = C, m = 2 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrine;
- when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical 3-4 di-hydroxy substituted benzyl, T_1 = CO and the free valence of A is saturated with OH, the percursor drug of R is known as 2-amino,(3,4-dihydroxyphenyl)propanoic acid (dopa).

3. Compounds according to claims 1-2, wherein when in formula (I) b0 = 0, Y in the bivalent linking group C is selected between Y_P and Y_{AR} as above defined.

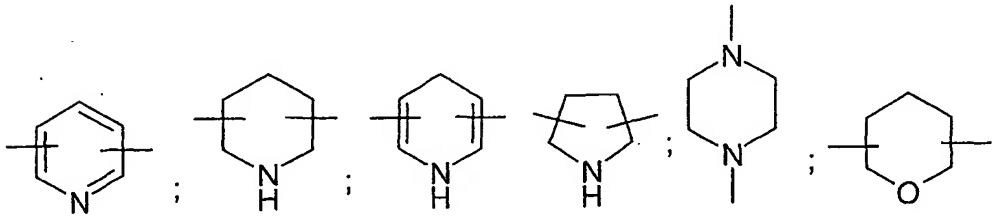
4. Compounds according to claim 3, wherein Y^3 is selected from the following bivalent radicals:

(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)

(Y19)



(Y7) (Y8) (Y9) (Y10) (Y11) (Y18)



(Y12) (Y13) (Y14) (Y15) (Y16) (Y17)

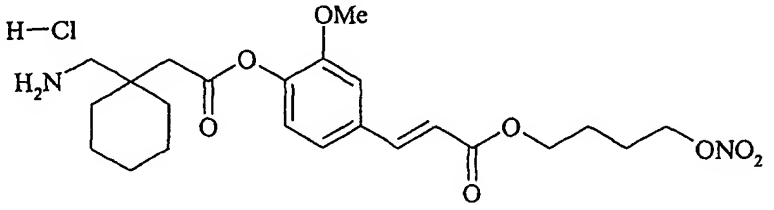
5. Compounds according to claim 4, wherein Y^3 is selected from (Y12), having the two free valences in the ortho position with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted; ; (Y19), wherein the free valence on the ring is found in para position to the nitrogen atom.

6. Compounds according to claims 1-5, wherein in formula (I) the precursors of B are the following: ferulic acid, N-

acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid.

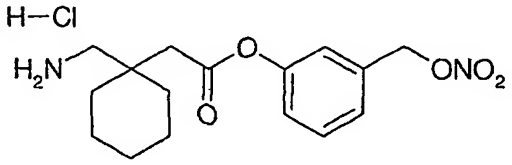
7. Compounds according to claims 1-6, wherein the precursor drugs are selected from gabapentine, norvaline, arginine, pregabaline, (S)3-isobutylGABA, agmatine.

8. Compounds according to claims 1-7, selected from the following: 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



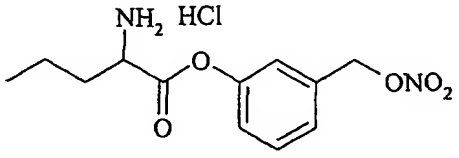
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



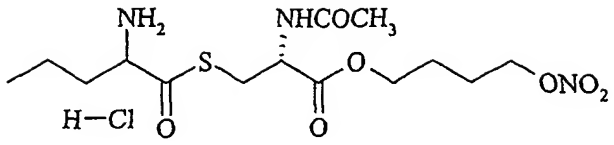
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



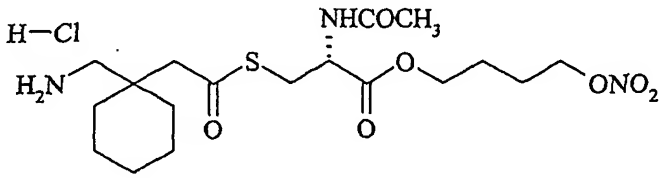
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino pentanoate hydrochloride (XVIII)



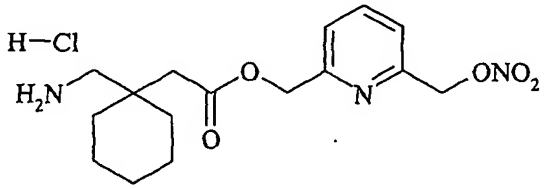
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl) cyclohexanacetate hydrochloride (XIX)



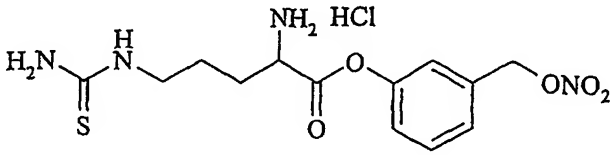
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



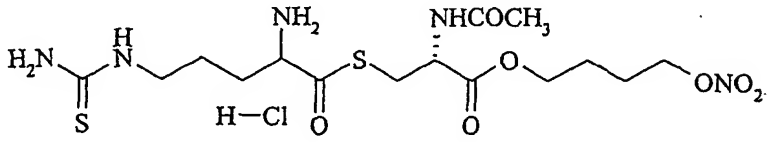
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



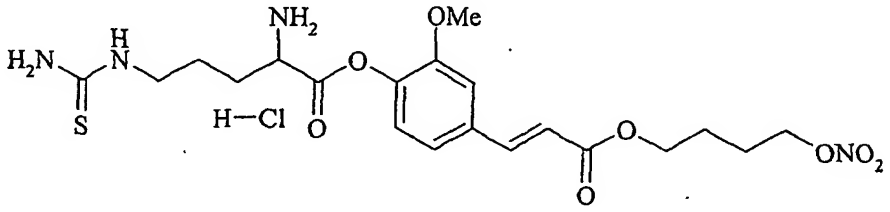
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



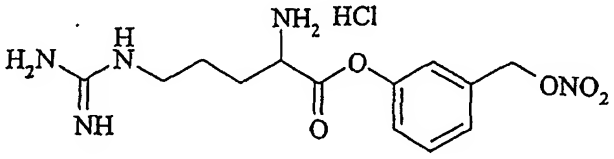
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



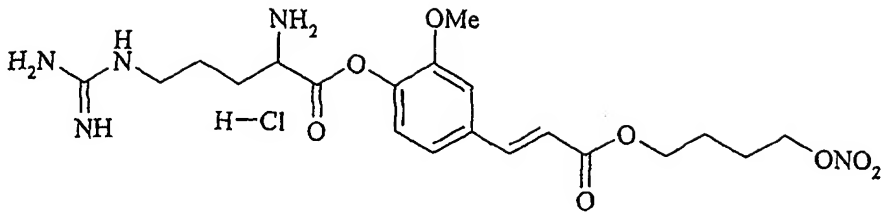
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



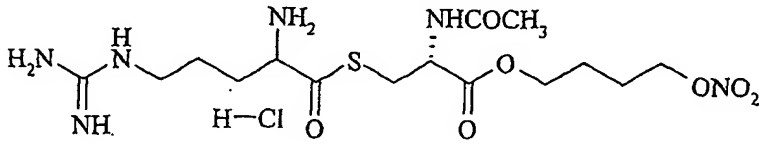
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



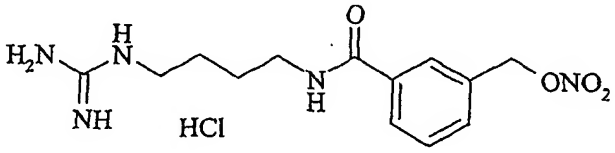
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



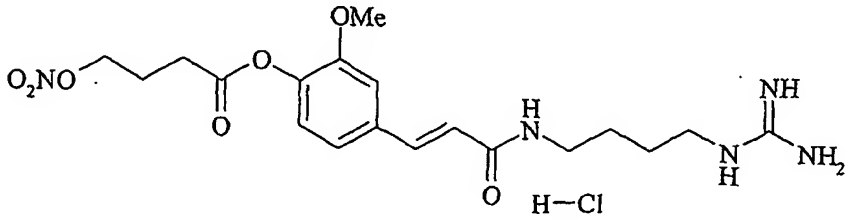
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



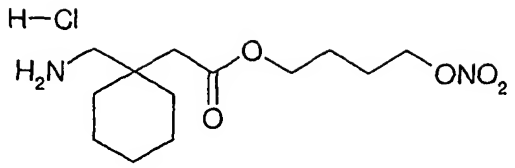
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)] phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy) butyl hydrochloride ester (XXIX)



(XXIX)

9. Compounds according to claims 1-8, as nitrate salts.

10. Compounds according to claims 1-9, in combination with NO donor compounds.

11. Compounds according to claim 10, wherein the NO donor compounds contain in the molecule radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen.

12. Pharmaceutical compositions for parenteral, oral and topical use comprising the compounds according to claims 1-11.

13. Compounds according to claims 1-12, for use as medicament.

14. Use of the compounds according to claims 1-13, for preparing drugs for epilepsy.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 C07C229/28 C07C229/08 C07C327/22 C07C335/08
C07D213/30 C07C279/14 C07C279/12 A61K31/195 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199614 Derwent Publications Ltd., London, GB; Class B02, AN 1996-136303 XP002213051 & JP 08 027154 A (NIPPON KAYAKU KK), 30 January 1996 (1996-01-30) abstract	1,12-14
X	WO 00 54756 A (UNIV KINGSTON) 21 September 2000 (2000-09-21) page 3, line 27; claims 1,42	1,12-14
X	US 5 883 122 A (BENNETT BRIAN M ET AL) 16 March 1999 (1999-03-16) column 2, line 5; claims 1-13	1,12-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 2002	03. 12. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CA 1 322 958 A (BOLGER GORDON T) 12 October 1993 (1993-10-12) page 1, line 18; claim 1	1,12-14
X	US 5 719 186 A (MUSSO DAVID LEE ET AL) 17 February 1998 (1998-02-17) column 3, line 63; claims 1,2	1,12-14
X	EP 0 372 998 A (BEECHAM GROUP PLC) 13 June 1990 (1990-06-13) abstract; claim 1	1,12-14
X	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) claim 1	1,12
X	WO 95 09831 A (NICOX LTD ;DEL SOLDATO PIERO (IT)) 13 April 1995 (1995-04-13) cited in the application abstract; claim 1	1,12
X	WO 97 16405 A (NICOX SA ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 9 May 1997 (1997-05-09) cited in the application claims 1-6	1,12
X	WO 01 12584 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 February 2001 (2001-02-22) cited in the application abstract; claims 1-13	1,12
X	WO 00 61537 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) claims 1-10	1,12
X	WO 00 61604 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) claims 1-12	1,12
P,X	WO 02 30867 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 18 April 2002 (2002-04-18) claim 1	1,12
P,X	WO 02 30866 A (NICOX SA ;ANTOGNAZZA PATRIZIA (IT); DEL SOLDATO PIERO (IT); BENEDI) 18 April 2002 (2002-04-18) claims 1-8,10	1,12

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KAWASHIMA ET AL: "Synthesis and Pharmacological Evaluation of (Nitrooxy)alkyl Apovincaminates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, 1993, pages 815-819, XP002210204 ISSN: 0022-2623 page 819, column 1; table 1	1,12
X	CIRINO G ET AL: "INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE EXPRESSION BY NOVEL NONSTEROIDAL ANTI-INFLAMMATORY DERIVATIVES WITH GASTROINTESTINAL SPARING PROPERTIES" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 117, no. 7, April 1996 (1996-04), pages 1421-1426, XP000938504 ISSN: 0007-1188 abstract	1,12
X	OGAWA T ET AL: "SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITIES OF NEW 1,4-DIHYDROPYRIDINE DERIVATIVES CONTAINING NITROOXYALKYLESTER MOIETIES AT THE 3- AND 5-POSITIONS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 6, no. 41, June 1993 (1993-06), pages 1049-1054, XP001093850 ISSN: 0009-2363 page 1054, column 1, paragraph 2; tables I-III	1,12
A	WO 00 44705 A (NICOX SA ;DEL SOLDATO PIERO (IT); GARUFI MICHELE (IT)) 3 August 2000 (2000-08-03) abstract; example 1	8
A	WO 98 42661 A (YISSUM RES DEV CO ;HAJ YEHIA ABDULLAH (IL)) 1 October 1998 (1998-10-01) claims 1-10	8
A	WO 98 09948 A (NICOX SA ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 12 March 1998 (1998-03-12) abstract, page 46 to page 48	8
A	WO 00 51988 A (NICOX SA ;DEL SOLDATO PIERO (IT); BENEDINI FRANCESCA (IT)) 8 September 2000 (2000-09-08) claims 1,9-13; examples 1-15	8

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1-7,9-14
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-14 partially

   compounds having the following common structural feature: -(CH2)3-ONO2 useful for preparing drugs for epilepsy

2. Claims: 1-14 partially

   compounds having the following common structural feature: phenyl-CH2-ONO2 substituted in meta position, useful for preparing drugs for epilepsy

3. Claims: 1-14 partially

   compounds having the following common structural feature: 2-NO2-O-CH2-pyridyl which is substituted in the 6 position with the group -CH2-O-(CO)-, useful for preparing drugs for epilepsy

Continuation of Box I.2

Claims Nos.: 1-7,9-14

Present claims 1-7, 9-14 relate to an extremely large number of possible compounds/uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 8 and of the examples 1-4.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty, only a few of them have been cited in the search report. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the compounds of claim 8 and of the examples 1-4 as abovementioned.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/EP 02/06389

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